PATENT COOPERATION TREATY

PCT

NOTIFICATION OF TRANSMITTAL OF COPIES OF TRANSLATION OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 72.2)

From the INTERNATIONAL BUREAU

To:

HUBER, Bernard
Huber & Schüssler
Truderinger Strasse 246
D-81825 München
ALLEMAGNE

Date of mailing (day/month/year) 05 December 2001 (05.12.01)	
Applicant's or agent's file reference M 4357 Wd	**IMPORTANT NOTIFICATION**
International application No. PCT/DE00/00232	International filing date (day/month/year) 26 January 2000 (26.01.00)
Applicant MICE & MORE GMBH & CO. KG et al	

1. Transmittal of the translation to the applicant.

The International Bureau transmits herewith a copy of the English translation made by the International Bureau of the international preliminary examination report established by the International Preliminary Examining Authority.

2. Transmittal of the copy of the translation to the elected Offices.

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following elected Offices requiring such translation:

JP,US

The following elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

EP

3. Reminder regarding translation into (one of) the official language(s) of the elected Office(s).

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report.

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Maria KIRCHNER
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference M 4357 Wd	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DE00/00232	International filing date (*day/month/year*) 26 January 2000 (26.01.00)	Priority date (*day/month/year*) 28 January 1999 (28.01.99)

International Patent Classification (IPC) or national classification and IPC
C12N 15/00, A01K 67/027, C07K 14/82, A61K 49/00

Applicant
MICE & MORE GMBH & CO. KG

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23 August 2000 (23.08.00)	09 April 2001 (09.04.2001)
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE00/00232

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-10, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages 1-16, filed with the letter of 04 December 2000 (04.12.2000)

☒ the drawings:

pages 1/9-9/9, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE00/00232

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-18.

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE00/00232

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☒ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. _____

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: BOXES II, III and IV

1. Citations

This report makes reference to the following search report citations. Documents D8 and D9 were not indicated in the international search report. Copies of those documents are attached. The same numbering will be used in the further proceedings:

D1: TZENG, Y.J. ET AL.: "SV40 T/t-antigen induces premature mammary gland involution by apoptosis and selects for p53 missense mutation in mammary tumors", ONCOGENE, Vol. 16, No. 16, 23 April 1998 (1998-04-23), pages 2103-2114

D2: ROBINSON, G.W. ET AL.: "Understanding mammary gland development through the imbalanced expression of growth regulators", DEVELOPMENTAL DYNAMICS, Vol. 206, No. 2, 1996, pages 159-168

D3: WO-A-97/39117 (UNIV. LIVERPOOL; RUDLAND PHILIP SPENCER (GB)); BARRACLOUGH BARRY ROG), 23 October 1997 (1997-10-23)

D4: JÄGER, R. ET AL.: "Overexpression of Bcl-2 inhibits alveolar cell apoptosis during involution and accelerates c-myc-induced tumorigenesis of the mammary gland in transgenic mice", ONCOGENE, Vol. 15, No. 15, 9 October 1997 (1997-10-09), pages 1787-1795

D5: VAN DER MOST, R. G. ET AL.: "Analysis of cytotoxic T cell response to dominant and subdominant epitopes during acute and chronic lymphocytic choriomeningitis virus infection", JOURNAL OF IMMUNOLOGY, Vol. 157, 1996, pages 5543-5554

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: BOXES II, III and IV

D7: SCHULTZ-GARG, C. ET AL.: "A transgenic mouse model for the ductal carcinoma in situ of the mammary gland", ONCOGENE, Vol. 19, No. 8, 21 February 2000 (2000-02-21), pages 1028-1037

D8: Tzeng, Yien-Jen et al.: "Breast cancer formation in transgenic animals induced by the whey acidic protein SV40 T antigen (WAP-SV-T) hybrid gene", Oncogene, Vol. 8, 1993, pages 1965-1971

D9: Santarelli, R. et al.: SV40 T-antigen induces breast cancer formation with a high efficiency in lactating and virgin WAP-SV-T transgenic animals but with a low efficiency in ovariectomized animals", Oncogene, Vol. 12, 1996, pages 495-505.

2. **Content of the application**

The present application concerns transgenic mice containing a gene that can be activated by lactotropic hormones and showing an inducible ductal carcinoma *in situ* (DCIS). It describes mice who express the SV-40 T-antigen and the n118 epitope of the LCM-virus under the control of a "whey acidic protein" (WAP) promoter. It also describes methods for producing these mice and their use for diagnostic purposes.

3. **Box III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: BOXES II, III and IV

3.1 Claims 1-18 concern mammals without further definition, that is without excluding humans, and their production. They therefore concern a subject matter which, in the opinion of the Examiner, falls under PCT Rule 67.1(iv). Consequently, no opinion is established with regard to the industrial applicability of the claimed subject matter (PCT Article 34(4)(a)(i)).

4. **Box IV**

Lack of unity of the invention

The different inventions are:

1) Claims 1-5 (partly), 7-13 (partly), 15-18 (partly)
WAP-T1 mouse, methods for producing and using the mouse for examining DCIS or developing therapeutic agents for DCIS.

2) Claims 1-5 (partly), 7-13 (partly), 15-18 (partly)
WAP-T2 mouse, methods for producing and using the mouse for examining DCIS or developing therapeutic agents for DCIS.

3) Claims 1-5 (partly), 7-13 (partly), 15-18 (partly)
WAP-T10 mouse, methods for producing and using the mouse for examining DCIS or developing therapeutic agents for DCIS.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: BOXES II, III and IV

4) Claims 1-5 (partly), 6, 7-13 (partly), 15-18 (partly)
WAP-T-NP6, WAP-T-NP8, WAP-T-NP10 mice, methods for producing and using the mice for examining DCIS or developing therapeutic agents for DCIS.

For the following reasons, these inventions are not so linked so as to form a single general inventive concept (PCT Rule 13.1):

Independent Claims 1, 9, 17 and 18 concern transgenic mice with inducible ductal carcinoma *in situ* containing an activatable oncogene, preferably a gene encoding for the SV40 T-Ag gene under the control of the WAP-promoter, methods for producing the mice and therapeutic uses.

The technical relationship between the claimed mice is that they are all characterised by inducible DICS and contain an oncogene that can be activated by lactotropic hormones.

D1 describes transgenic mice who express the SV40 T antigen under the control of the WAP promoter. The analysis of those mice shows that they develop a carcinoma of the female mammary gland (page 2103; the abstract; pages 2104-2105). The same argument could also have been put forth on the basis of the content of D2.

As a result, the subject matter of independent Claim 1 and hence also the technical relationship between the independent claims is already known.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: BOXES II, III and IV

The unity of invention required by PCT Rule 13.1 is therefore no longer established, since there is no technical relationship between the subjects of the above-mentioned inventions involving one or more of the same or corresponding special technical features (PCT Rule 13.2).

Since the literature does not describe WAP-T-NP mice who specifically express the n118 epitope of the nucleoprotein of the LCM virus, the different mouse lines (WAP-T-NP-6, WAP-T-NP-8 and WAP-T-NP-10) are regarded as a single invention.

The applicant was invited to indicate which of the above-mentioned inventions should be examined and to restrict the claims accordingly or pay additional fees.

The applicant has paid under protest the examination of the four inventions and at the same time submitted new claims. Since this is not provided for in the PCT procedure, the originally submitted claims were examined. Furthermore, an analysis of the newly submitted claims indicated that the objections raised to the original set of claims apply *mutatis mutandis* to the new set of claims, and therefore this set also lacks unity of invention, although it is subdivided into other groups of claims.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	6, 8, 14, 16-18	YES
	Claims	1-5, 7, 9-13, 15	NO
Inventive step (IS)	Claims	8, 16-18	YES
	Claims	1-7, 9-15	NO
Industrial applicability (IA)	Claims		YES
	Claims	1-18: no opinion	NO

2. Citations and explanations

5.1 D1 and D2 describe WAP-SV40-T/t transgenic mice who express the SV40-T/t antigen under the control of the WAP promoter and have been generated with the same WAP-SV40 T-Ag construct as the claimed animals (as shown by the applicant himself in the subsequently published document D7; see page 1036 and "Material and Methods"). Since the WAP promoter is specifically activated by lactotropic hormones (such as oestrogen, progesterone, prolactin, insulin and glucocorticoids), the expression of the SV40 T-Ag can be specifically induced by these hormones when they are secreted in the body of the transgenic animals (e.g. during pregnancy or the lactation period).

In D1, the analysis of the mice shows that they develop a carcinoma of the female mammary gland after their first lactation (page 2103; the Abstract; pages 2104-2105). Consequently, D1 already describes mammals with inducible ductal carcinoma and containing an oncogene activatable by lactotropic hormones (see also the other publications of the same working group: D8, pages 1965-1968; and D9: pages 497-499).

It is known to a person skilled in the art (and also described in D7, page 1036) that when transgenic mice are produced, a palette of phenotypes can always be produced, depending on the genetic background of the mice used, the integration site of the transgene and the number of copies of the transgene. It can therefore be expected that when sufficient transgenic animals are analysed each phenotype will be represented. Even if in D1 the WAP-T-Ag transgenic mice have not been histologically examined for DCIS specifically, at least some of these mice must have shown this specific preliminary stage of mammary carcinoma, since those mice are characterised by exactly the same technical features as the WAP-T-Ag mice of the application.

Claim 4 concerns an oncogene with a "strong T-cell epitope". This expression is vague and also comprises to a person skilled in the art the SV40-T antigen, since this epitope can also induce a specific immune reaction. The content of D1 is therefore prejudicial to the novelty of Claims 1-5 and 7 (PCT Article 33(1) and (2)).

5.2 D3 describes different transgenic animals and corresponding cell lines. It describes, *inter alia*, rats who express a transgenic MMTVLTR-TGFa gene. The MMTVLTR promoter, like the WAP promoter, is specific to the mammary gland and is activated by the hormones secreted during pregnancy. The rats who express the TGFa oncogene were histologically examined and show different types of tumours, *inter alia* DICS, or also more advanced tumours (page 51, line 26 - page 55, line 28). The same applies to the

MMTVLTR-c-erb-2 transgenic animals, some of whom also show DICS (page 55, line 28 - page 59, line 20; and Fig. 8f).

D3 is therefore prejudicial to the novelty of the subject matter of Claims 1, 2 and 7 (PCT Article 33(1) and (3)).

In addition, D3 also describes MMTVLTR-tsA58 transgenic animals who express the SV40 T antigene in the mammary gland, depending on temperature; however, the analysis of the phenotype of those animals is not more extensively described (page 21, line 25 - page 29, line 18).

5.3 The production of transgenic mice is a standard method well known to the experts and which today no longer presents any technical difficulties. The production of transgenic animals who express an oncogene is also described in D8 (page 1970), D3 (page 13, lines 15-30) and D4 (page 1793). As already mentioned, in D3 the MMTVLTR-TGFa transgenic animals were also screened for DCIS.

Consequently, the subject matter of Claims 9-13 and 15 is not novel (PCT Article 33(1) and (2)).

5.4 Claims 6 and 14 concern transgenic mice who express a fusion protein comprising the SV40 T-Ag and the n118 epitope of the LCM virus, as well as their production.

Such transgenic animals are not described in the prior art.

The subject matter of Claims 6 and 14 is therefore novel (PCT Article 33(1) and (2)).

Even if D1-D4 describe transgenic mice who express an oncogene, none of those documents suggests the specific production of transgenic mice who express a n118 epitope of the LCM virus. Nevertheless, for the following reasons, it is not clear to what extent the subject matter of Claims 6 and 14 involves an inventive step (PCT Article 33(3)):

The object of the application appears to be the production of a transgenic animal model for examining DICS. The question is raised of what are the advantages of the transgenic animals who express the n118 epitope in comparison with animals who express only the SV40 T-Ag, and of whether they make any additional contribution to the solution of the problem, since no significant difference can be recognised between the phenotypes of the WAP-T-NP and WAP-T mice.

The subject matter of Claims 6 and 14 therefore does not appear for the time being to be inventive (PCT Article 33(1) and (3)).

5.5 Claims 17 and 18 concern the use of these transgenic mice for examining DCIS and for developing diagnostic markers and therapeutic agents.

Even if transgenic mice having the same technical features as the claimed mice are known from the prior art (see above), these mice have never been recognised as animal models for DCIS. In the citations D1-D4 the focus of the analysis of the

transgenic animals lies on mature mammary carcinoma, rather than on the earlier stages of the diseases. Consequently, the use of these mice for screening for DCIS is novel and inventive (PCT Article 33(1)-(3)).

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

6.1 Contrary to PCT Rule 5.1(a)(ii), the description does not cite documents D1-D3 and does not indicate the relevant prior art disclosed therein.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

7.1 The expression used in Claims 4 and 1, "strong T-cell epitope", is vague and unclear and leaves the reader in doubt about the meaning of the technical feature in question. As a result, the definition of the subject matter of these claims is not clear (PCT Article 6).

7.2 The expression "nl18 epitope" used in Claims 6 and 14 does not have a generally recognised meaning. As a result, the definition of the subject matter of these claims is not clear. These claims should indicate the sequence of this epitope (PCT Article 6).

Moreover, the pWAP-T-NP DNA has not been deposited (PCT Rule 13bis), contrary to the applicant's statement on page 7, lines 23-27. The examiner could not find in the DSMZ the DSM number indicated. The different mouse lines have not been deposited either.

7.3 Claims 8 and 16 contain references to the figures. PCT Rule 6.2(a) stipulates that the claims may contain references only when absolutely necessary, which is not the present case. Moreover, these claims concern mice and their production, although the figures to which these claims refer only show cells.